S/N 09/096,749 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Shohei Koide	Examiner: Larry R. Helms, Ph.D.
Serial No.:	09/096,749	Group Art Unit: 1642
Filed:	June 12, 1997	Docket: 109.034US1
Title:	ARTIFICIAL ANTIBODY POLYPEPTIDES	

Declaration of Shohei Koide under 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

I, Shohei Koide, Ph.D, declare and say as follows:

1. I am the inventor of the above-referenced U.S. Patent Application.

2. In addition to the examples presented in the original filing, I have performed additional experiments that further support the pending claims. I prepared mutant FNfn10 proteins that contain glycine insertions or glycine-rich insertions in the AB, BC, CD, DE, EF or FG loops. Glycines and the glycine-rich sequence (Gly-Gly-Met-Gly-Gly) were chosen to be inserted because glycine insertions are generally highly destabilizing. Glycines have a high degree of conformational freedom (large entropy) in the unrestrained state. It is thus energetically unfavorable to restrain glycines by folding of a protein, because of a high entropic penalty. Therefore these insertion mutations are expected to provide useful guidelines as to whether these loops can be extensively modified for the engineering of binding proteins.

3. Mutant proteins were prepared using the Kunkel mutagenesis or polymerase chain reaction (PCR) metagenesis methods, and the conformational stability was determined using guanidine hydrochloride-induced denaturation, as described in (Koide, A., Bailey, C. W., Huang, X. & Koide, S. (1998) The fibronectin type III domain as a scaffold for novel binding proteins. *J. Mol. Biol. 284*, 1141-1151). Figure 1 attached to the present Declaration shows effects of these mutations on the conformational stability of FNfn10. Specifically, Figure 1 depicts denaturation curves of FNfn10 and its variants containing additional glycine residues in one or more loops.

Denaturation reactions were monitored using tryptophan fluorescence and analyzed according to the two-state model, as described in Koide *et al.* (1998). Experiments were performed in 10 mM sodium citrate buffer pH 6.0 containing 100 mM sodium chloride at 30 °C (the AB, BC, DE and FG insertions) or in 20 mM sodium phosphate buffer pH 7.0 containing 100 mM sodium chloride (the CD and EF loop insertions). The conformational stability of these molecules do not significantly change between the two set of measurement conditions.

4. The following Table A summarizes the free energy of unfolding in the absence of guanidine hydrochloride.

Table A: Effects of glycine insertions on the conformational stability of FNfn10

Protein	ΔG (kcal/mol)
Wild Type	7.70±0.09
Four glycines in the FG loop	6.91±0.15
Eight glycines in the FG loop	6.62±0.11
Four glycines in the DE loop	5.66±0.21
Four glycines in the BC loop and eight glycines in the FG loop	6.09±0.17
Four glycines in the AB loop	8.23±0.09
Gly-Gly-Met-Gly-Gly insertion in the CD loop	7.87±0.18
Gly-Gly-Met-Gly-Gly insertion in the EF loop	6.32±0.10

These results show that some of the insertions decrease the stability of FNfn10, but these mutant proteins still retain sufficient degrees of conformational stability to remain folded. For example, even the least stable protein (the DE loop mutant) is more than 99.99% folded in the buffer solution. Thus, these results demonstrate that it is feasible to make mutant proteins in which the loops of the FNfn10 protein contain deletions, insertions and replacements.

5. **Selection of AB-loop monobodies that bind to the human estrogen receptor α**

Additional monobodies were created that have variable AB-loop regions. The following protocol was used:

Materials: 17β-estradiol (E2) was purchased from Sigma. An anti-LexA antibody was kindly provided by Dr. E. Golemis (Fox Chase Cancer Center). Secondary antibodies were purchased from Pierce. The ERα cDNA clone was kindly provided by the late Dr. A. Notides (University of Rochester Medical Center).

Strains and media: Yeast strains EGY48, *MATα his3 trp1 ura3 leu2::6LexAop-LEU2*, and RFY206, *MATa his3Δ200 leu2-3 lys2Δ201 trp1Δ::hisG ura3-52*, have been described (Gyuris *et al.*, *Cell 75*, 791-803 (1993); Finley & Brent, *Proc. Natl. Acad. Sci. USA 91*, 12980-12984 (1994)) and were purchased from OriGene Technologies (Rockville, MD). Yeast was grown in YPD media or YC dropout media following instructions from Origene Technologies (The DupLEX-A™ Yeast Two-Hybrid System Manual). Manipulation of *Escherichia coli* was according to Sambrook *et al.* (Sambrook *et al.*, Molecular Cloning: A laboratory manual, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor (1989)).

Construction of yeast two-hybrid vectors and a monobody library: The method of Brent and others in vector construction was essentially followed (Mendelsohn & Brent, *Curr. Opin. Biotechnol. 5*, 482-486 (1994); Golemis & Serebriiskii, Two-hybrid system/interaction trap in *Cells: A laboratory manual* Ed.) pp69.1-40, CSH Laboratory Press, Cold Spring Harbor, NY (1997); Colas & Brent, *Trends Biotechnol. 16*, 355-363 (1998)). The synthetic gene for FNfn10 (Koide *et al.*, *J. Mol. Biol. 284*, 1141-1151 (1998)) was subcloned in the plasmid pYESTrp2 (Invitrogen, Carlsbad, CA) so that FNfn10 is fused C-terminal to the B42 activation domain (pYT45). The plasmid encoding a LexA-fusion protein of residues 297-595 of ERα was constructed by subcloning the ERα gene fragment in the plasmid pEG202 (Origene Technologies) using standard PCR cloning methods (pEGERα297-595). Although ERα itself has a weak transcriptional activation function in yeast (Chen *et al.*, *Biochem. Pharmacol. 53*, 1161-1172 (1997)), these constructs did not activate the *LEU2* reporter gene to an extent that confers *LEU*$^+$ phenotype in the yeast EGY48.

A monobody library was constructed by inserting seven diversified residues between Pro15 and Thr16 in the AB loop (residue numbering according to Koide *et al.*, *J. Mol. Biol. 284*, 1141-1151 (1998)). The DNA segment corresponding to these seven residues of FNfn10 in the plasmid pYT45 was randomized using the NNS codon (N denotes a mixture of A, T, G, C, and S denotes a mixture of G and C) by Kunkel mutagenesis (Kunkel *et al.*, *Methods Enzymol. 154*,

367-382 (1987)). The yeast strain EGY48 was transformed with this plasmid to produce a library containing approximately $2x10^6$ independent clones.

Library screening: The yeast strain RFY206 harboring pEGERα297-595 and a *LacZ* reporter plasmid, pSH18-34 (Origene Technologies), was mated with EGY48 containing the monobody library as described previously (Finley & Brent, *Proc. Natl. Acad. Sci. USA 91*, 12980-12984 (1994)). Diploid cells that contain an ERα-binding monobody were selected using the *LEU*$^+$ phenotype on minimal dropout media (Gal Raf –leu –his –ura –trp). The library screening was performed in the presence of 1 μM E2. Colonies grown after three days of incubation at 30 °C were further tested for galactose-dependence of the *LEU*$^+$ phenotype and β-galactosidase activity. The plasmids coding for a monobody were recovered from yeast clones following instructions supplied by Origene Technologies, and the amino acid sequences of monobodies were deduced by DNA sequencing.

β-Galactosidase assay: Quantitative assays were performed as follows. The yeast strain RFY206 was first transformed with pEGERα297-595 and pSH18-34 and subsequently with a derivative of the pYT45 plasmid encoding a particular monobody. Yeast cells were grown overnight at 30°C in the YC Glc –his –ura –trp media. The culture was then spun down, the media were discarded, and the cells were resuspend in YC Gal Raf –his –ura –trp media containing a ligand at a final cell density of 0.2 OD_{660nm} in a total volume of 175 μl in the wells of a deep 96-well plate. The ligand (E2) concentration was 1 μM. After incubating for six hours at 30°C with shaking, 175 μl of β-galactosidase assay buffer (60mM Na_2HPO_4, 40mM NaH_2PO_4, 10mM KCl, 1mM $MgSO_4$, 0.27% β-mercaptoethanol, 0.004% SDS, 4mg/ml 2-nitrophenyl-β-D-galactosidase, 50% Y-PER (Pierce Chemical Co., Rockford, IL)) was added to the culture, incubated at 30°C, then the reaction was stopped by adding 150 μl of 1M Na_2CO_3. After centrifugation, OD_{420} was measured and the β-galactosidase activity was calculated. *See*, attached Figure 2.

6. The results of the protocol in ¶ 5 above were the following. Two clones that bind to the E and F domain of the human estrogen receptor α (ERα) were obtained from the screening. Their amino acid sequences are shown below.

	amino acid sequence in the AB loop
wild type	P_{15}-------T_{16}
library	PXXXXXXXT
clone A1	WTWVLRE
clone B1	WVLITRS

In this table, "–" denotes a gap in the wild-type sequence where an additional residue was inserted in the library, and "X" denotes a diversified position in the library. Quantitative β-galactosidase assays were performed. It has been shown that β-galactosidase activity is well correlated with the strength of the interaction in the yeast two-hybrid system (Estojak *et al.*, *Mol. Cell. Biol.* 15:5820-5829 (1995)). The two selected monobodies bind to ERα in the presence of E2 but not in the absence of E2, indicating a high degree of binding specificity of these monobodies. In contrast, the wild-type Fn3 showed no detectable binding to ERα in the absence or presence of E2.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

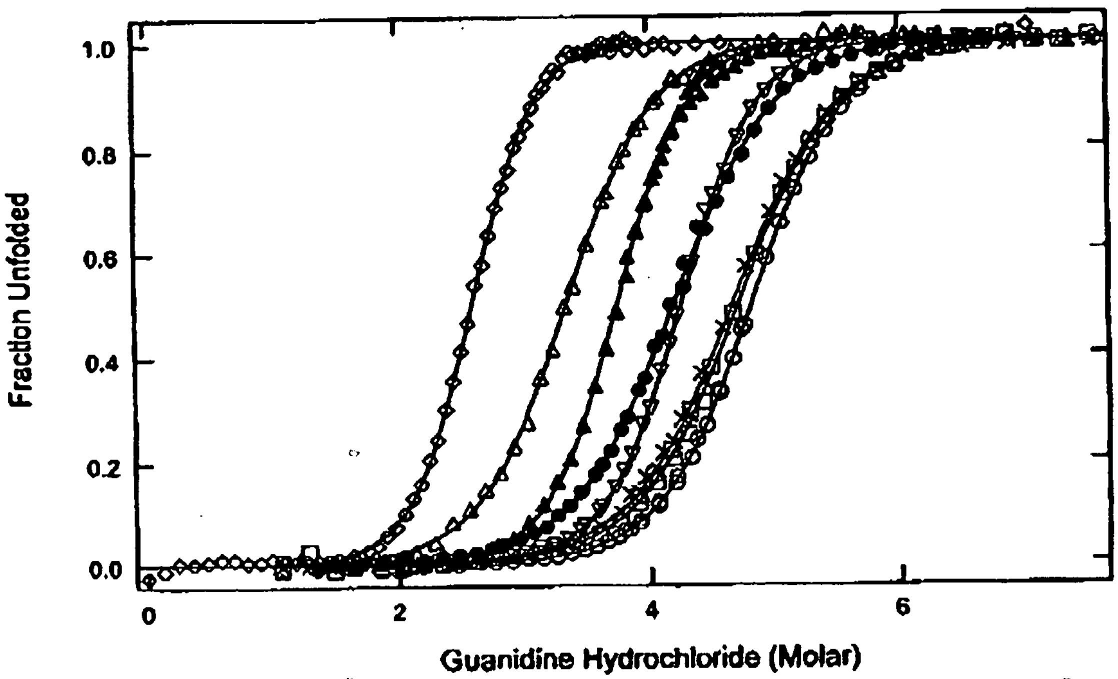
Date *October 23, 2001* By *Shohei Koide*
Shohei Koide, Ph.D.

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on October ___, 2001.

Name

Signature

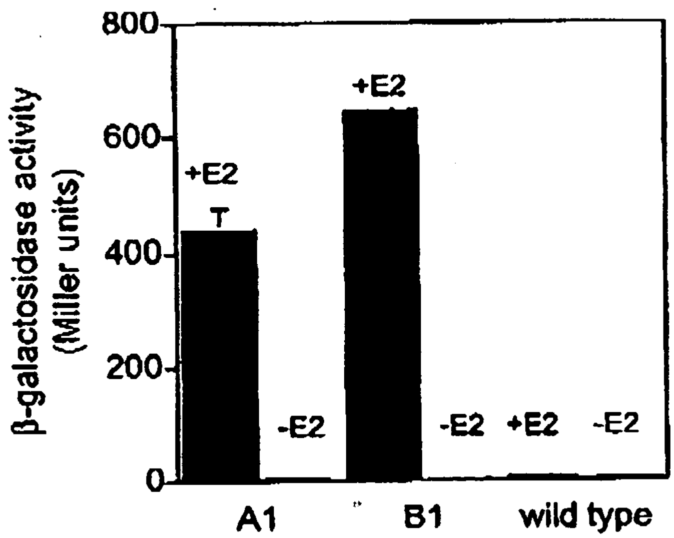
Figure 1



Guanidine hydrochloride-induced unfolding of FNfn10 mutants. The fraction of unfolded molecule is plotted as a function of guanidine hydrochloride concentration.

- ○ Wild Type
- ▽ AB loop 4 gly insertion
- ● BC loop 4 gly insertion & FG loop 8 gly insertion
- ▲ CD loop gly-gly-met-gly-gly insertion
- △ DE loop 4 gly insertion
- ◇ EF loop gly-gly-met-gly-gly insertion
- □ FG loop 4 gly insertion
- × FG loop 8 gly insertion

Figure 2


800
600
400
200
0
β-galactosidase activity
(Miller units)
+E2
-E2
+E2
-E2
+E2
-E2
A1
B1
wild type

Appendix

Landis on Mechanics of Patent Claim Drafting

Fourth Edition

Robert C. Faber

G1-1025
Practising Law Institute
New York City

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Dedication

This book is dedicated to the faculty of PLI claim-drafting tutors, who have given most generously of their time and talents in the patent bar review course, helping the students to draft better claims. The book is also dedicated to Ruth Druss, Program Attorney of PLI and founder of the PLI patent and patent bar review courses, and to Carol Faber, who encouraged the writing.

I must also dedicate this book to my partners in Ostrolenk, Faber, Gerb & Soffen, who have always set the highest standards of professionalism in all respects.

But the highest tribute goes to John L. Landis, the author of the first two editions of this book, who so thoroughly covered and so clearly presented the material that writing this edition was a pleasure.

always a "member," throughout all claims depending on the same claim in which the element has been first named. In a claim which does not depend from one naming an element, another name may be used for the same element. For example, in one chain of claims, the element may be the broader "surface," while in another chain of claims, the element may be the narrower "anvil" of which the surface is only a part. Within each claim chain, the name of the element may never change. The "member" cannot sometimes be an "element," that is, it cannot be a "connecting element." An "element" would be a different claimed structure.

Often, an element is described not only by the noun, e.g., "member," but by adjectives which modify the noun, as "connecting member" or "left side connecting member." After any feature is first named completely with all its adjectives in a claim, subsequent mentions of the feature in that claim or in subsequent dependent claims in the claim chain, following the first naming of the element, must use the same noun for that element, but may use fewer than all of the adjectives, thereafter calling it "member" or "connecting member," without the other adjectives "left side." The only limit on this freedom to drop adjectives is that there must be no other element whose designation, when shortened either to the noun alone or to the noun plus fewer than all of its adjectives, would be identified by the same words, because that would cause confusion as to which element was meant. Further, in a chain of claims following the one that first uses an adjective, the adjective cannot change. It may be deleted, as just noted, but not changed. If it is "an upper engaging member," it cannot later be "the upper holding member" or the "top engaging member."

For clarity in claim writing, I recommend avoiding use of first, second, third, etc., as the adjective which distinguishes one element from another. This usage is proper and so long as the adjective is used consistently, it cannot be considered ambiguous. However, sometimes a more descriptive adjective, descriptive, e.g., as to function or location or major characteristics (left side, elongate, etc.) might help the claim reader determine which element is being identified. On the other hand, the elements designated first, second, third, etc. may be identical in structure and function and may be distinguishable only by a nondescriptive adjective, or maybe using a descriptive adjective would, in the

drafter's opinion, impermissibly narrow the scope of the recited element. Further, reciting only the adjectives first, second, etc. is useful where there are two or more ways of arranging elements and the claim writer wishes to encompass all of the ways, so that one location or arrangement would be first and the other would be second, without specifiying which is which. Each element must always be described in such a distinctive manner as to clearly distinguish it from other similar or identical elements, as covered in section 16. Use the same terminology in the specification, as in the claims, even to at least once identifying the claimed elements using their distinguishing adjective, i.e., first or second, base or connector, etc.

Summary

Select a clear name for each element, based on the detailed specification description where given. Where a broad scope name is desired, functional names, such as "a fastener" or "means for moving . . . ," should be used.

§ 20 Plural Elements

The number of elements of a given type, if more than one, should also be stated where the number is material to the claim:

A pair of arms . . .

Three springs . . .

A plurality of rods . . . (used for an indefinite number, two or more). [The word "multiplicity" is often used also, but this may tend to connote a fairly large number, such as "a sieve having a multiplicity of perforations."]

At least five fingers . . . (used where there must be at least five but more would do).

The minimum (or as appropriate, maximum) number of elements necessary for the combination to function properly should be recited. The minimum number then covers a larger number where, as is customary, the word "comprising" is used (section 7). The term "a pair" will cover two or any number greater than two, but it will not cover only one. Where one or more will function,

then one merely claims "a" member (singular) and this covers more than one.

Optionally, one sees "at least one ________" or "at least two ________," or "at most three," which are also correct.

When claiming a combination, where more than one of a certain element is included in the combination (e.g., conveyor means), the term "at least two" means the minimum number of a particular element required.[9] This interpretation gives effect to the recitation of the two distinct elements in the claimed structure. Therefore, all claims would require two or more of the conveyor structure. Since laymen are eventually considering claim language, i.e., a judge or a jury, the latter option may now be preferable, since the nuanced meaning of "comprising" may not be so easily understood as "at least two . . . ," when a claim is meant to cover any number greater than one of a particular element. An alternative statement "one or more" would ordinarily be considered improper under the rule against alternative claiming discussed in section 24. However, one case[10] allowed a claim including "a spline or splines."

When there is a maximum number of a particular element in a claimed combination, the maximum is recited, e.g., "at most three."

Where the quantity of a particular element is not material to the claim, there is no benefit to reciting that there are a plurality of that element. Recite "a finger" and leave it at that, or "at least one finger," if the plurality of fingers is obviously present.

Some practitioners advocate naming the element and then following that with the word "means," such as "finger means." The latter phrasing is indefinite as to number and yet encompasses any number. However, once the word "means" is used in naming a claim element, it almost certainly will be treated as a means plus function element under 35 U.S.C. section 112, paragraph 6. Case

9. Lantech, Inc. v. Keip Machine Co., 27 U.S.P.Q.2d 1906 (W.D. Mich 1993), *rev'd in part, remanded,* 32 F.3d 542, 31 U.S.P.Q.2d 1666 (Fed. Cir. 1994) *and vacating, summary judgment granted,* 1995 U.S. Dist. LEXIS 11636 (W.D. Mich. 1995).

10. *In re* Pavlecka, 138 U.S.P.Q. (BNA) 118 (C.C.P.A. 1963).

precedents, discussed below in the section hereof on means clauses, may narrow the scope of means limitations, as compared with other limitations, whereby "finger means" may be more restricted in scope than "at least one finger," when a claim is interpreted for application to a possible infringement.

In an earlier claim, a single one of an element may be claimed. A later dependent claim may recite a plurality of those same elements, without redefining the features of the element, and the parent claim provides antecedent support for the dependent claim.[11] For example, claim 1 at section 14 above might have claimed "a leg. . ." or "at least one leg," while claim 2 could then recite "a plurality of the legs" or "at least two of the legs."

Summary

State the minimum number of similar elements needed where more than one is necessary to the claim. If any number more than one will do, use the phrase "a plurality."

§ 21 Double Inclusion of Elements

One should be careful that precisely the same element is not included in the claim twice under two different names. See section 19 about a consistent name for each element. This is an error known as "double inclusion."

Sometimes the problem arises in writing dependent claims (see section 11), where one might inadvertently add as an apparently new element something already in the parent claim or in one of several earlier claims in a chain of dependent claims. This is likely to occur in a complicated structure with many elements.

Sometimes the double recitation occurs because an element is recited broadly in an earlier claim and then mentioned in greater detail using a different name in a later claim. For example, claim 1 (section 14) calls for "means for oscillating the container." If claim 2 recited "A combination as recited in claim 1, *further comprising* a motor, . . ." it would be improper since the motor is part

11. *Ex parte* Moelands, 36 U.S.P.Q.2d (BNA) 1474, 1475 (Bd. Pat. Interp. 1987).

word "crafts" in conjunction with explanations to the effect that various handcrafted items are the product of various cottage industries, which can generally produce high quality handmade goods, albeit at a higher price than similar products produced using mass production machinery. This sort of use of "crafts" does not show that "COTTAGE CRAFTS" has a meaning identical to "cottage industry." The terms are not shown to be used interchangeably.

[3] The Examining Attorney has also submitted for the record an excerpt from the October 1, 1978 edition of the Washington Post, which states that in the Mexican countryside "there are still small studios, actually cottage crafts, where the whole family makes a certain thing * * *." This example equates the term "COTTAGE CRAFTS" with the term "small studios," not with the term 'cottage industry." Also submitted is an excerpt from the October 12, 1979 British Broadcasting Corporation Summary of World Broadcasts, the text of which states that India supplies the Soviet Union with "cottage crafts products." This is not a domestic publication, and as such it is not evidence of how the term is used in the United States. Although the quantity and variety of evidence concerning the meaning of "cottage industry" is substantial, these two relatively obscure examples of how the term "COTTAGE CRAFTS" is used are the only evidence as to the meaning of the term sought to be registered. There are no dictionary definitions of "COTTAGE CRAFTS," and no other examples from any books or periodicals. Applicant, for its part, has made of record the pertinent parts of seven dictionaries and encyclopedias dealing with the textile industry, none of which list "COTTAGE CRAFTS" as a term with a meaning in this area of commerce.

Based on the record before us we do not find that "COTTAGE CRAFTS" has any descriptive or misdescriptive significance as applied to bedspreads, quilts, and the other goods set forth in the application. It is at most suggestive of the goods. Because we find the mark to be suggestive rather that misdescriptive, we need not reach the question of whether or not anyone would be deceived by the use of this term on these goods. There is no evidence on this point in the record anyway. We do not have to ask whether the misrepresentation would materially affect the decision to purchase the goods, since a refusal under Section 2(a) was not made. Nor do we have to decide applicant's claim under Section 2(f).

Decision

The refusal to register is reversed. The evidence of distinctiveness will remain in the file, but, the request for registration under the provisions of Section 2(f) has been stricken, since it is unnecessary.

Patent and Trademark Office Board of Appeal

Ex Parte Cole, Howarth, and Reading

Opinion dated May 31, 1983

PATENTS

1. Claims — Duplicate or redundant (§20.40)

Nothing in 35 USC 112 prohibits minor overlap of claims within four corners of same application.

2. Patentability — Utility (§51.75)

There is no requirement that each compound within claim be equally useful for each contemplated application.

3. Specification — Sufficiency of disclosure (§62.7)

Compliance with 35 USC 112 must be adjudged from perspective that claims are addressed to person of average skill in particular art, who would not choose combination of circumstances that would render claimed composition or method inoperative.

Particular Patents — Clavulanic acid

Cole, Howarth, and Reading, Esters of Clavulanic Acid, rejection of Claims 1-445 reversed.

Appeal from Art Unit 122.

Application for patent of Martin Cole, Thomas T. Howarth, and Christopher Reading, Application Serial No. 726,224, filed Sept. 24, 1976, division of application, Serial No. 569,007, filed Apr. 17, 1975. From decision rejecting Claims 1-445, applicants appeal (Appeal No. 490-47). Reversed.

Albert L. Jacobs, Jr., New York, N.Y., for applicants.

Before Sturtevant and Milestone, Examiners-in-Chief, and French, Acting Examiner-in-Chief.

Sturtevant, Examiner-in-Chief.

This is an appeal from the final rejection of all claims in the application. Claim 445, the last claim in the case, was not included in Appellants' Notice of Appeal. However, both the Examiner and counsel have treated it as included and we have done so as well.

Claims 36-38, 83 and 120 are reproduced here to illustrate the subject matter:

36. A B-lactamase inhibitory ester of clavulanic acid.

37. A non-toxic hydrolyzable ester of clavulanic acid.

38. An ester of clavulanic acid capable of being converted to clavulanic acid or a salt thereof by hydrolysis or hydrogenolysis.

83. A pharmaceutical composition useful for treating bacterial infections in humans and animals which comprises an antibacterially effective amount of a pharmaceutically acceptable clavulanic acid ester which is hydrolyzable in vivo, in combination with a pharmaceutically acceptable carrier.

120. A method of treating bacterial infections in humans and animals which comprises administering to a human or animal in need thereof an antibacterially effective amount of a pharmaceutical composition which comprises an antibacterially effective amount of a pharmaceutically acceptable clavulanic acid ester which is hydrolyzable in vivo, in combination with a pharmaceutically acceptable carrier.

There is no art relied on. The only issue before us is whether or not all the claims comply with the requirements of 35 USC 112, paragraphs one and two. The Examiner lists eight points in support of his rejection, but not one of these points specifies claims 40-42, 44, 45, 55-58, 60 or 62-66. Despite the Examiner's omissions we have considered each of the claims on appeal vis-a-vis each of the points discussed in the Examiner's Answer. The eight points appear in the Answer (Paper No. 29) at pages 2-9 and we shall not recite them here.

[1] After careful review of the entire record we find no merit in any of the Examiner's contentions and we therefore reverse his decision. With regard to his first point, there is nothing in the statute (35 USC 112) prohibiting minor overlap of claims within the four corners of the same application. With regard to the fourth point we find the disclosure especially at page 11 fully sufficient to support compounds with an ester moiety of more than 16 carbons, even though they may not be preferred. As to the fifth point, we must totally disagree with the Examiner's position: We consider hydrolysis and hydrogenolysis, in the context of the claimed invention here, very well recognized techniques. As to the sixth and seventh points, we are in full agreement with Appellants' counter-argument as set forth in their Reply Brief (Paper No. 31) at the paragraph bridging pages 2-3.

As to the Examiner's point No. 2, the definition of the moiety NR^2R^3 in claim 39 is sufficiently clear, in context, so that the person of merely average skill in this art will not be led astray as theorized by the Examiner. We suggest that this entire issue might have been very simply resolved by omitting the phrase "wherein R^2 and R^3 are as above defined" at lines 5-4 from the end of claim 39. Indeed, it is suggested that such an amendment would be desirable even now.

Respecting the Examiner's third point, i.e. support for claims 311 through 444, we agree with Appellants that these claims are sufficiently supported in the disclosure at page 12. In addition we call attention to original claim 35, which must of course be considered as part of the original disclosure. Appeal claim 445 is substantially the same as that original claim and claims 311-355 depend directly thereon. The remaining claims of this series depend either on composition claim 67 or method claim 103, both of which also define substantially the same Markush group of esters as original claim 35.

[2] Finally, we have difficulty following the Examiner's reason in support of his eighth contention. The passage at page 105 of the specification, on which the Examiner relies to support his doubts of utility, is clearly insufficient. We know of no statutory or case law requiring each and every compound within a claim to be equally useful for each and every contemplated application. As pointed out by Appellants, the results presented at page 105 of the disclosure merely indicate that two of Appellants' claimed esters failed to inhibit the growth of one pathogen at the concentration. At page 90 of the specification results are given showing "broad spectrum activity" of one of these two esters. At page 106 antibacterial activity is clearly demonstrated for the other.

[3] With respect to all eight of the bases for the Examiner's rejection we direct the Examiner's attention to the following: In re Smith et al., 481 F.2d 910, 178 USPQ 620 (CCPA 1973) and In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). Claims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some

combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination. See also In re Geerdes, 491 F.2d 1260, 180 USPQ 789 (CCPA 1974).

REVERSED

Patent and Trademark Office
Trademark Trial and Appeal Board

Alpha Industries, Inc.
v. Alpha Microsystems

Decided Jan. 23, 1984

TRADEMARKS

1. Evidence — Judicial notice (§67.335)

Opposition — Consideration of marks of third party (§67.573)

TTAB will not take judicial notice of third-party applications and, in absence of evidence of actual use of third-party registered marks, such registrations are entitled to little weight.

Trademark opposition No. 64,340, by Alpha Industries, Inc., against Alpha Microsystems, applications, Serial Nos. 240,497, filed No. 26, 1979, and 242,157, filed Dec. 10, 1979. On applicant's request for reconsideration. Request denied.

See also 220 USPQ 67.

Charles Heiken, Waltham, Mass., for Alpha Industries, Inc.

Blakely, Sokoloff, Taylor & Zafman, Beverly Hills, Calif., for Alpha Microsystems.

Before Allen, Frugé, and Simms, Members.

Simms, Member.

Applicant has filed a request for reconsideration of the decision issued September 1, 1983 sustaining the opposition and refusing registration to applicant. Opposer has filed a brief in opposition to the request for reconsideration.

Among other things, applicant argues that the Board improperly found prior use by opposer of the mark ALPHA when any such rights which may have existed in opposer were abandoned since 1974. The mark ALPHA appeared on some of opposer's microwave products (semiconductors or diodes) (Andrew Kariotis dep., 46; opposer's exhibit 5, Section F). The word ALPHA also appeared prominently in some of opposer's advertisements (opposer's exhibit 9). Opposer's testimony also reveals reasons (the minute size of microwave components and customer and government specification) why no marks may have appeared on some of opposer's products (Andrew Kariotis dep., 45, 49, 53, 68). In any event, the name ALPHA has appeared and continues to appear prominently as part of opposer's trade name on or in connection with the promotion and sale of opposer's microwave parts, and purchasers over the years have variously referred to opposer as Alpha, Alpha Microwave and Alpha Industries (Andrew Kariotis dep., 64-65, 68-69, 112).

[1] In its request, applicant has disputed the Board's treatment of the numerous copies of third-party registrations relied upon by applicant. It appears that applicant is requesting the Board to take judicial notice of the statements made in each of the underlying third-party applications that the registered marks had been in use in commerce and, with respect to the registrations which bear evidence of the filing of an affidavit under Section 15 of the Act, the verified statements of the continued use of those marks residing in those registration files. The Boad will not take judicial notice of such documents and, in the absence of evidence of actual use of the third-party registered marks, the Board believes that the registrations are entitled to little weight.

Applicant's arguments concerning the sophistication of the purchasers and the lack of evidence of actual confusion have been treated in the Board's opinion. Finally, we disagree that the Board "misallocated the burden of proof." We believe that, by a preponderance of the evidence, opposer has established its priority and the likelihood of confusion.

Accordingly, applicant's request for reconsideration is denied.

Court of Appeals, Seventh Circuit

American Can Company v. Mansukhani et al.

No. 83-2553

Decided July 30, 1984. As amended Aug. 10, 1984

UNFAIR COMPETITION

1. Injunction — Preliminary injunction (§40.5)

Federal district that could have issued ex parte order directing accused trade secret misappropriator to be prepared in immediate hearing to show cause why order, permitting sampling of accused's goods and disclosure of documents, should not be entered, abused its discretion by issuing ex parte temporary restraining order authorizing trade secret owner's employees, with assistance of U.S. Marshalls, to enter accused's premises to take samples of its products and allow for copying its documents.

2. Injunction — Unfair competition (§40.9)

Injunctive orders based on standard of functional or practical similarity between trade secret owner's inks and accused misappropriator's, and adding up to permanent injunction against selling inks that are "compositionally similar" to trade secret owner's and that can be "attributed principally" to use of trade secrets, reflect standard too vague for case involving trade secrets whose scope was narrowly confined by public information and by accused misappropriator's own knowledge and experience.

Appeal from District Court for the Eastern District of Wisconsin, Warren, J.

Action by American Can Company, against Ishwar Mansukhani, doing business as Brand Associates, and Ruth Brand, doing business as Brand Associates, and Brand M, Inc., for breach of confidential relationship and unauthorized use or disclosure of trade secrets. From order granting preliminary injunction, defendants appeal. Reversed and remanded.

See also 216 USPQ 1094 and 220 USPQ 167.

Andrew. O. Riteris, and Michael, Best & Friedrich, both of Milwaukee, Wis., for appellants.

Douglas W. Wyatt, and Wyatt, Gerb Shoup, Scobey & Badie, both of New Yor N.Y., for appellee.

Before Wood, Cudahy, and Flaum, Circ Judges.

Cudahy, Circuit Judge.

This is an appeal from the district cour preliminary injunction enjoining defenda from taking actions which might constit misappropriation of plaintiff's trade secre The appeal presents several important pro dural issues involving the use of ex pa temporary restraining orders in trade sec cases. The appeal also involves the scope a necessary precision of injunctive relie trade secret cases. At the heart of the ca the problem that courts face in framing or to prevent defendants from competing un ly by using another's trade secrets while s permitting defendants to compete fairly usi public information and their own talents a experience.

I

Facts

Plaintiff-appellee American Can Comp ("American Can") develops, manufactu and sells commercial jet inks. Commercial inks are sprayed onto a printing surface wi out direct contact, and they are theref useful for printing on delicate surfaces other surfaces for which contact printing unsuitable. For example, some of the cc mercial jet inks involved in this case are u to print date codes on aluminum beer c to print on plastic antifreeze jugs.

Defendants-appellants are Ishwar sukhani, his wife, Ruth Brand, and .. businesses, Brand Associates and Brand Inc. Mansukhani is an experienced ink ch ist, and his wife is also a physical chen although she had no experience with i until she and her husband started their b nesses in late 1980.

The relationship between plaintiff and fendants goes back to August 1976. At time, American Can had a wholly ow subsidiary called M & T Chemicals, ("M & T"), which was engaged in the c mercial jet ink business. M & T hired M sukhani as a chemist; at that time, he experienced in ink chemistry but had hac experience with jet inks. He signed an ag ment with M & T promising not to us

of Law will be entered on the same date herewith.

ORDER AND JUDGMENT

In accordance with the Findings of Fact and Conclusions of Law entered on the same date herewith,

IT IS HEREBY ORDERED AND ADJUDGED, as follows:

1. The Nolan patent (No. 4,506,189), issued on March 19, 1985, is a valid patent.

2. By the manufacture, production, sale and distribution of its SAF-T-COTE fluorescent lamp, Trojan has infringed the Nolan patent.

3. By virtue of this infringement, Shat-R-Shield is entitled to injunctive relief. Trojan shall immediately cease and desist from the manufacture, production, sale and distribution of the SAF-T-COTE fluorescent lamp.

4. Trojan shall recall all the SAF-T-COTE fluorescent lamps sold to and still in the possession of its customers.

5. The Court having determined that Trojan's infringement was not willful and wanton, Shat-R-Shield is not entitled to treble damages.

6. Shat-R-Shield shall have no accounting for monetary damages.

7. The Court having found that this is not an exceptional case, Shat-R-Shield is not entitled to its attorney's fees.

8. All claims having been resolved as to all parties herein, this action is now DISMISSED and STRICKEN from the docket.

9. There being no just reason for delay, this is a FINAL and APPEALABLE Order and Judgment.

Court of Appeals, Federal Circuit

In re Wands

No. 87-1454

Decided September 30, 1988

PATENTS

1. **Patentability/Validity — Adequacy of disclosure (§115.12)**

Data disclosed in application for immunoassay method patent, which shows that applicants screened nine of 143 cell lines developed for production of antibody necessary to practice invention, stored remainder of said cell lines, and found that four out of nine cell lines screened produced antibody falling within limitation of claims, were erroneously interpreted by Board of Patent Appeals and Interferences as failing to meet disclosure requirements of 35 USC 112, since board's characterization of stored cell lines as "failures" demonstrating unreliability of applicants' methods was improper in view of fact that such unscreened cell lines prove nothing concerning probability of success of person skilled in art attempting to obtain requisite antibodies using applicants' methods.

2. **Patentability/Validity — Adequacy of disclosure (§115.12)**

Disclosure in application for immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring "undue experimentation," even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or "hybridomas," since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one "experiment" is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent of Jack R. Wands, Vincent R. Zurawski, Jr., and Hubert J. P. Schoemaker, serial number 188,735. From decision of Board of Patent Appeals and Interferences affirming rejection of application, applicants appeal. Reversed; Newman, J., concurring in part and dissenting in part in separate opinion.

Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein (Henry N. Wixon, with them on brief), Washington, D.C., for appellant.

John H. Raubitschek, associate solicitor (Joseph F. Nakamura and Fred E. McKelvey, with him on brief), PTO, for appellee.

Before Smith, Newman, and Bissell, circuit judges.

Smith, J.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM Antibodies," which was filed September 19, 1980.[1] The rejection under 35 U.S.C. §112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

I. *Issue*

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. §112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

II. *Background*

A. *The Art.*

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an antigen. The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure of an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as reagents for sensitive diagnostic tests (*e.g.*, to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay*.

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes*. Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. There are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are *lymphocytes*. Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.

Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma

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[1] *In re Wands*, Appeal No. 673-76 (Bd. Pat. App. & Int. Dec. 30, 1986).

cells that are all progeny of a single cell) are called monoclonal antibodies.[2]

B. *The Claimed Invention.*

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. §112, first paragraph, a hybridoma cell line hat secretes IgM antibodies against HBsAg the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available o the public when the '145 patent issued.

The application on appeal claims methods or immunoassay of HBsAg using monoclonal antibodies such as those described in he '145 patent. Most immunoassay methods ave used monoclonal antibodies of the IgG otype. IgM antibodies were disfavored in ie prior art because of their sensitivity to educing agents and their tendency to selfaggregate and precipitate. Appellants found at their monoclonal IgM antibodies could used for immunoassay of HbsAg with iexpectedly high sensitivity and specificity. laims 1, 3, 7, 8, 14, and 15 are drawn to ethods for the immunoassay of HBsAg ing high-affinity IgM monoclonal antidies. Claims 19 and 25–27 are for chemilly modified (*e.g.*, radioactively labeled) onoclonal IgM antibodies used in the as- ys. The broadest method claim reads:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:

contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and

determining the presence of said substance in said sample;

wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

Certain claims were rejected under 35 U.S.C. §103; these rejections have not been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25–27 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. *Analysis*

A. *Enablement by Deposit of Micro-organisms and Cell Lines.*

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention."[3] A patent need not disclose what is well known in the art.[4] Although we review underlying facts found by the board under a "clearly erroneous" standard,[5] we review enablement as a question of law.[6]

Where an invention depends on the use of living materials such as microorganisms or

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[2] For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368–71, 231 USPQ 81, 82–83 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987).

[3] *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

[4] *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

[5] *Coleman v. Dines*, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed. Cir. 1985).

[6] *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 875 (1987); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960 n.6, 220 USPQ 592, 599 n.6 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 [225 USPQ 232] (1984).

cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues.[7] Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112.[8] A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public.[9] Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials.[10]

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the prima facie date of invention,[11] and to satisfy the requirement under 35 U.S.C. §114 that the PTO be guaranteed access to the invention during pendency of the application.[12] Although a deposit may serve these purposes, we recognized, in *In re Lundak*,[13] that these purposes, nevertheless, may be met in ways other than by making a deposit.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. *Undue Experimentation.*

Although inventions involving microorganisms or other living cells often can be enabled by a deposit,[14] a deposit is not always necessary to satisfy the enablement requirement.[15] No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.[16] Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case.[17]

Appellants contend that their written specification fully enables the practice of

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[7] *In re Argoudelis*, 434 F.2d 1390, 1392–93, 168 USPQ 99, 101–02 (CCPA 1970).

[8] *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985); *Feldman v. Aunstrup*, 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), *cert. denied*, 424 U.S. 912 [188 USPQ 720] (1976); Manual of Patent Examining Procedure (MPEP) 608.01 (p)(C) (5th ed. 1983, rev. 1987). *See generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. Trademark Off. Soc'y 569 (1985).

[9] *In re Jackson*, 217 USPQ 804, 807–08 (Bd. App. 1982) (strains of a newly discovered species of bacteria isolated from nature); *Feldman*, 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); *In re Argoudelis*, 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); *In re Kropp*, 143 USPQ 148, 152 (Bd. App. 1959) (newly discovered microorganism isolated from soil).

[10] *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

[11] *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95–96; *In re Feldman*, 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis*, 434 F.2d at 1394–96, 168 USPQ at 103–04 (Baldwin, J. concurring).

[12] *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95–96; *In re Feldman*, 517 F.2d at 1354, 186 USPQ at 112.

[13] *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95–96.

[14] *In re Argoudelis*, 434 F.2d at 1393, 168 USPQ at 102.

[15] *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

[16] *Id.* at 1186–87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co.*, 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J. 1967); *Guaranty Trust Co. v. Union Solvents Corp.*, 54 F.2d 400, 403–06, 12 USPQ 47, 50–53 (D. Del. 1931), *aff'd*, 61 F.2d 1041, 15 USPQ 237 (3d Cir. 1932), *cert. denied*, 288 U.S. 614 (1933); MPEP 608.01(p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

[17] *In re Jackson*, 217 USPQ at 807; *see In re Metcalfe*, 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

their claimed invention because the mono- clonal antibodies needed to perform the im- munoassays can be made from readily avail- ible starting materials using methods that ire well known in the monoclonal antibody irt. Wands states that application of these nethods to make high-affinity IgM anti- HBsAg antibodies requires only routine creening, and that does not amount to un- lue experimentation. There is no challenge o their contention that the starting materi- ls (i.e., mice, HBsAg antigen, and myeloma ells) are available to the public. The PTO oncedes that the methods used to prepare ybridomas and to screen them for high- ffinity IgM antibodies against HBsAg were ither well known in the monoclonal anti- ody art or adequately disclosed in the '145 atent and in the current application. This is onsistent with this court's recognition with spect to another patent application that ethods for obtaining and screening mono- onal antibodies were well known in 1980.[18] he sole issue is whether, in this particular se, it would require undue experimentation produce high-affinity IgM monoclonal tibodies.

Enablement is not precluded by the neces- y for some experimentation such as rou- ie screening.[19] However, experimentation eded to practice the invention must not be due experimentation.[20] "the key word is idue,' not 'experimentation.' "[21]

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878–79; 169 USPQ 759, 762–63 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 172 USPQ 257] (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, f it is merely routine, or if the specifica- ion in question provides a reasonable mount of guidance with respect to the direction in which the experimentation should proceed ° ° °.[22]

The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.[23] Whether undue experi- mentation is needed is not a single, simple factual determination, but rather is a conclu- sion reached by weighing many factual con- siderations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*.[24] They in- clude (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or ab- sence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.[25]

In order to understand whether the rejec- tion was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immu- nize an animal. The '145 patent provides a detailed description of procedures for immu- nizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lympho- cytes are separated from the other spleen cells. The lymphocytes are mixed with mye- loma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the de- sired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and mye- loma cells. The cells are cultured in a medi-

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Hybritech, 802 F.2d at 1384, 231 USPQ at

Id.; Atlas Powder Co. v. E.I. DuPont De ours & Co., 750 F.2d 1569, 1576, 224 USPQ 413 (Fed. Cir. 1984); *In re Angstadt*, 537 at 502–504, 190 USPQ at 218; *In re Geerdes*, F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA); *Mineral Separation, Ltd. v. Hyde*, 242 261, 270–71 (1916).

Hybritech, 802 F.2d at 1384, 231 USPQ at W.L. Gore, 721 F.2d at 1557, 220 USPQ at

In re Colianni, 561 F.2d 220, 224, 195 USPQ 153 (CCPA 1977) (Miller, J., concurring).

In re Angstadt, 537 F.2d at 504, 190 USPQ 9.

[22] *In re Jackson*, 217 USPQ at 807.

[23] *See Hybritech*, 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder*, 750 F.2d at 1576, 224 USPQ at 413.

[24] *Ex parte Forman*, 230 USPQ at 547.

[25] *Id.; see In re Colianni*, 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer*, 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

um in which all the lymphocytes and mye- loma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce suffi- cient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.

Wands used a commercially available ra- dioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioac- tivity bound gives some indication of the strength of the antibody-antigen binding, but does not yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies sat- isfy all of the limitations of appellants' claims, the antibodies require further screen- ing to select those which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1}.[26] The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

During prosecution Wands submitted a declaration under 37 C.F.R §1.132 provid- ing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybrido- mas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial ra- dioimmunoassay, were classified as "high binders." Using this criterion, 143 high-bind- ing hybridomas were obtained. In the decla- ration, Wands stated that[27]

It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity (Ka [greater than] 10^9 M^{-1}) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.

The PTO has not challenged this statement.

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screen- ing. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were sub- jected to further analysis. Four (three from one fusion and one from another fusion) fell within the claims, that is, were IgM anti- bodies and had a binding affinity constant of at least 10^9 M^{-1}. Of the remaining five anti- bodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declara- tion explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. §1.56 that applicants fully dis- close all of their relevant data, and not just favorable results.[28] How these stored hybri- domas are viewed is central to the positions of the parties.

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies with a binding affinity constant of at least 10^9 M^{-1}. Thus, only 4 out of 143 hybridomas, or 2.8 percent, were *proved* to fall within the claims. Fur- thermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appel- lants' methods were not predictable or repro- ducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to

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[26] The examiner, the board, and Wands all point out that, technically, the strength of anti- body-HBsAg binding is measured as *avidity*, which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Never- theless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high- affinity" as essentially synonymous with "having a binding affinity constant of at least 10^9 M^{-1}."

[27] A table in the declaration presented the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than 10^9 M^{-1}.

[28] *See Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 220 USQ 98 (Fed. Cir. 1983).

engage in undue experimentation in order to make antibodies that fall within the claims.

Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least 10^9 M^{-1}. Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that produce IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide some support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed to make them.

The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions. Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. §1.132 stating that after the patent application was submitted they performed an eleventh fusion experiment and obtained another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that fit all of the limitations of their claims.

[1] We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable.[29] At worst, they prove nothing at all about the probability of success, and merely show that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

[2] When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.[30]

IV. *Conclusion*

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. §112, first paragraph, is reversed.

REVERSED

Newman, J., concurring in part, dissenting in part.

A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.

Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987). I agree that it is not necessary that there be a deposit of multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. §112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims. Wands' claims on appeal include the following:

> 19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least 10^9 M^{-1}.
>
> 26. Monoclonal high affinity IgM antibodies immunoreactive with hepatitis B surface antigen.

Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.

Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)

Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove the right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experi-

[29] Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

[30] *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

ments in genetic engineering produce, at best, unpredictable results", quoting from *Ex parte Forman*, 230 USPQ 546, 547 (Bd.Pat.App. and Int. 1986).

The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. §112. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970).

As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); *In re Cook*, 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971). The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1971); *In re Rainer*, 347 F.2d 574, 146 USPQ 218 (CCPA 1965); *Ex parte Forman*, 230 USPQ at 547. Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

Patent and Trademark Office
Trademark Trial and Appeal Board

In re Johanna Farms Inc.

Serial No. 542,343

Decided June 30, 1988

JUDICIAL PRACTICE AND PROCEDURE

1. Procedure — Prior adjudication — In general (§410.1501)

Trademark Trial and Appeal Board's prior decision upholding examiner's refusal to register proposed mark "La Yogurt" does not preclude registration of mark pursuant to subsequent application, since applicant, by presenting survey evidence and consumer letters regarding issue of how purchasers perceive proposed mark, has demonstrated that instant factual situation is different from situation presented in prior proceeding.

TRADEMARKS AND UNFAIR TRADE PRACTICES

2. Types of marks — Non-descriptive — Particular marks (§327.0505)

Term "La Yogurt," with "yogurt" disclaimed, is registrable, since word "yogurt" is common English generic term rather than corruption or misspelling of French word for yogurt, since examining attorney failed to meet burden of showing clear evidence of generic use of mark as whole, and since evidence of record, including survey and consumer letters to applicant, demonstrates that primary significance of "La Yogurt" to majority of relevant public is that of brand name rather than generic term.

3. Registration and its effects — Federal registration — Procedure, form and content — Disclaimer (§315.0303.10)

Types of marks — Non-descriptive — Particular marks (§327.0505)

French article "La" combined with English generic term in proposed mark "La Yogurt" changes commercial impression of mark as whole and renders it registrable, since applicant's competitors would have no need to use "La Yogurt" mark as whole, other than to trade on applicant's good will, in view of applicant's disclaimer of word "yogurt."

Appeal from refusal of registration (Mark Traphagen, trademark examining attorney, Paul Fahrenkopf, managing attorney).

Related decisions: 222 USPQ 607, 223 USPQ 459.

Application of Johanna Farms Inc. for registration of trademark, serial no. 542,343, filed June 11, 1985. From decision refusing registration, applicant appeals. Reversed; Simms, Member, dissenting in separate opinion.

Lerner, David, Littenberg, Krumholz & Mentlik, Westfield, N. J., for applicant.

Before Sams, Rich, Rooney, Simms, Krugman, Cissel, Seeherman, and Hanak, members.

Krugman, Member.

An application has been filed by Johanna Farms, Inc. to register the term "LA YOGURT" ("YOGURT" disclaimed) as a trademark on the Principal Register for yogurt.[1] Applicant seeks registration pursuant to Section 2(f) of the Trademark Act based on the claim that the designation sought to be registered has acquired distinctiveness.

Registration has been refused on two grounds. First, the Examining Attorney maintains that registration herein is barred under the doctrine of stare decisis in view of a final decision rendered by the Board in connection with a prior application to register "LA YOGURT" for yogurt.[2] The Examining Attorney maintains that the relevant circumstances involved in the present case are identical to those considered in the prior application and that applicant is precluded from relitigating issues which have already been determined.

As a second ground for refusal, the Examining Attorney asserts that, even if it is determined that stare decisis does not bar registration herein, the phrase "LA YOGURT" is a generic designation, incapable of distinguishing applicant's goods from those of others; that "YOGURT" is the French generic name for the goods; that use of the French article "LA" in combination with "YOGURT" yields only an ungrammatical variation on the foreign generic term for the goods and that evidence of de facto secondary meaning cannot elevate the generic term sought to be registered to the status of a registrable trademark.

Applicant has appealed.

In view of the issues presented by this case, the oral hearing on November 17, 1987 was held before the eight members of the Trademark Trial and Appeal Board sitting, by designation of the Chairman of the Trademark Trial and Appeal Board, as an augmented panel.

Turning first to the issue of stare decisis, a brief review of the circumstances of the prior application and the Board's decision relating thereto are in order.

Applicant initially filed an application to register "LA YOGURT" as a trademark for yogurt on the Principal Register.[3] After registration was refused on the ground that the term sought to be registered was "merely the name of the goods," applicant amended its application to one seeking registration on the Supplemental Register. Eventually, registration was finally refused on the Supplemental Register on the ground that "LA YOGURT" was nothing more than the apt (generic) name of the goods and that said term, therefore, was unregistrable on the Supplemental Register. Applicant then appealed.

The Board, in deciding the appeal, noted that "yogurt" was concededly the name of the goods and that the term "la" had no significance by itself in relation to yogurt or any other product, other than as the French feminine article modifying the generic term. The Board then stated that the question to be decided was whether the entire term "LA YOGURT" was generic. If it were, the Board stated, the term could not be registered on either the Principal or Supplemental Register. If, however, "LA YOGURT" were not generic, it would be registrable on the Principal Register. In either case, the

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[1] Application Serial No. 542,343 filed June 11, 1985.

[2] In re Johanna Farms, Inc., 222 USPQ 607 (TTAB 1984), reconsideration denied, 223 USPQ 459 (TTAB 1984).

[3] Application Ser. No. 171,952 filed May 25, 1978.

his business, Studco, Inc., could produce I-studs. (Tr. 485, 578). Knorr then formed SSI and proceeded to make and sell infringing I-studs. (Tr. 532, 495-96). Knorr executed an agreement with Genstar (now Domtar), acting as agent for four other gypsum companies, to enable SSI to supply others with tabbed metal I-studs for use as a component in the Series V shaftwall systems. (Pl. Ex. 71, Tr. 532-34). Knorr and his businesses had been specifically warned that the use of the tabbed metal I-stud in a shaftwall may be covered by National Gypsum's patents in suit. (Pl. Ex. 71, para. 9).

SSI and Genstar then entered into a sublicense agreement which purported to allow SSI to use and sell the inventions covered by the patents in suit. (Pl. Ex. 87 and 90, Tr. 300-01). Without seeking legal advice as to the validity of this agreement, SSI began direct sales to all customers. (Tr. 303-07, 504). When National Gypsum sought to stop the infringing, Knorr asserted that all sales of the studs were sold and reported to Genstar. (Pl. Ex. 86, 89). At trial, Knorr admitted that the majority of studs were never sold to Genstar. (Tr. 552-55).

Knorr also concealed from National Gypsum that he and his businesses were short changing National Gypsum on royalty payments. (Tr. 544-48). Knorr attempted to cover up the sales by SSI of tabbed metal I-studs to Approved Equal, Inc., a related Knorr company. (Pl. Ex. 79, 160, Tr. 562-65).

[1] The court concludes that there is substantial evidence in the record to support a finding of willful infringement. Based on the totality of circumstances, this court finds that exceptional circumstances exist so as to justify an award of attorney fees to National Gypsum, the prevailing party.

This court will allow an award of attorney fees to National Gypsum for attorney fees it incurred asserting the Sauer, et al. patents.

Court of Appeals, Federal Circuit

In re O'Farrell

No. 87-1486

Decided August 10, 1988

PATENTS

1. Patentability/Validity — Obviousness — Evidence of (§115.0906)

Applicants' method of producing predetermined protein in stable form in host species of bacteria through genetic engineering is obvious within meaning of 35 USC 103 since reference, authored by two of three patent applicants and published more than one year prior to patent application date, contained detailed enabling methodology for practicing claimed invention, suggestion for modifying prior art to practice claimed invention, and evidence suggesting that invention could be successful, and reference thus rendered invention obvious to those of ordinary skill in art at time invention was made.

2. Patentability/Validity — Obviousness — Evidence of (§115.0906)

Experimenters' use of heterologous gene coded for ribosomal RNA, which is not ordinarily translated, rather than gene coded for predetermined protein, in plasmid cloning vector for introduction into host bacteria in genetic engineering experiment, does not require finding that applicant's claimed method of producing predetermined protein in host bacteria through genetic engineering was not obvious in view of published paper describing experiment, particularly observation that hybrid messenger RNA produced by experiment was apparently translated into protein, since it would have been obvious and reasonable to conclude from such observation that if gene coded for ribosomal RNA produced "junk" or "nonsense" protein, then use of gene coded for predetermined protein would result in production of "useful" protein, as application claims.

3. Patentability/Validity — Obviousness — In general (§115.0901)

Rejection of patent application cannot be overturned on ground that examiner and Board of Patent Appeals and Interferences applied impermissible "obvious to try" standard, since assignment of error for application of such standard usually occurs when invention is made by varying all parameters or trying each of numerous choices until successful without indication in prior art as to which parameters were critical or which choices were likely to be successful, or when invention is made by exploring promising new technology or general approach with only general guidance from prior art as to particular form of claimed invention or how to achieve it, and since neither situation is present in instant case.

4. Patentability/Validity — Obviousness — In general (§115.0901)

Finding of obviousness under 35 USC 103 requires only that prior art reveal reasonable expectation of success in producing claimed invention, rather than absolute prediction of such success.

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application, serial no. 180,424, filed by Patrick H. O'Farrell, Barry O. Polisky, and David H. Gelfand. From decision of Board of Patent Appeals and Interferences affirming final rejection of application on grounds of obviousness, applicants appeal. Affirmed.

J. Bruce McCubbrey of Fitch, Even, Tabin & Flannery (Virginia H. Meyer, with them on brief), San Francisco, Calif., for appellant.

Harris A. Pitlick, associate solicitor, Patent and Trademark Office (Joseph F. Nakamura, solicitor and Fred E. McKelvey, deputy solicitor, with him on brief), for appellee.

Before Markey, chief judge, and Rich and Nies, circuit judges.

Rich, J.

This appeal is from the decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (board) affirming the patent examiner's final rejection of patent application Serial No. 180,424, entitled "Method and Hybrid Vector for Regulating Translation of heterologous DNA in Bacteria." The application was rejected under 35 USC 103 on the ground that the claimed invention would have been obvious at the time the invention was made in view of a published paper by two of the three coinventors, and a publication by Bahl, Marians & Wu 1 *Gene* 81 (1976) (Bahl). We affirm.

The claimed invention is from the developing new field of genetic engineering. A broad claim on appeal reads:

Claim 1. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria comprising, providing a cloning vector which includes at least a substantial portion of a gene which is indigenous to the host species of bacteria and is functionally transcribed and translated in that species, said substantial portion of said indigenous gene further including the regulatory DNA sequences for RNA synthesis and protein synthesis but lacking the normal gene termination signal, and linking a natural or synthetic heterologous gene encoding said predetermined protein to said indigenous gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of said indigenous gene so that readthrough can occur from said indigenous gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Illustrative embodiments are defined in more specific claims. For example:

Claim 2. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria, comprising, providing an *E. coli* plasmid having an operator, a promoter, a site for the initiation of translation, and at least a substantial portion of the beta-galactosidase gene of the *E. coli* lactose operon, said substantial portion of said beta-galactosidase gene being under the control of said operator, promoter and site for initiation of translation, said substantial portion of said beta-galactosidase gene lacking the normal gene termination signal, and linking a heterologous gene encoding said predetermined protein to said beta-galactosidase gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of the said beta-galactosidase gene portion so that readthrough can occur from said beta-galactosidase gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Claim 3. The method of Claim 2 wherein said *E. coli* plasmid comprises the plasmid designated pBGP120.

Although the terms in these claims would be familiar to those of ordinary skill in genetic engineering, they employ a bewildering vocabulary new to those who are not versed in molecular biology. An understanding of the science and technology on which these claims are based is essential before one can analyze and explain whether the claimed invention would have been obvious in light of the prior art.

I. *Background* [1]

Proteins are biological molecules of enormous importance. Proteins include enzymes that catalyze biochemical reactions, major structural materials of the animal body, and many hormones. Numerous patents and applications for patents in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology projects, including appellants' claimed invention, is to devise methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

The basic organization of all proteins is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called *amino acids*, that are linked together covalently.[2] The chemical bonds linking amino acids together are called *peptide* bonds, so proteins are also called *polypeptides*.[3] It is the exact sequence in which the amino acids are strung together in a polypeptide chain that determines the identity of a protein and its chemical characteristics.[4] Although there are only 20 amino acids, they are strung together in different orders to produce the hundreds of thousands of proteins found in nature.

To make a protein molecule, a cell needs information about the sequence in which the amino acids must be assembled. The cell uses a long polymeric molecule, DNA (deoxyribonucleic acid), to store this information. The subunits of the DNA chain are called *nucleotides*. A nucleotide consists of a nitrogen-containing ring compound (called a *base*) linked to a 5-carbon sugar that has a phosphate group attached.[5] DNA is composed of only four nucleotides. They differ from each other in the base region of the molecule. The four bases of these subunits are adenine, guanine, cytosine, and thymine (abbreviated respectively as A, G, C and T). The sequence of these bases along the DNA molecule specifies which amino acids will be inserted in sequence into the polypeptide chain of a protein.

DNA molecules do not participate directly in the synthesis of proteins. DNA acts as a permanent "blueprint" of all of the genetic information in the cell, and exists mainly in extremely long strands (called *chromosomes*) containing information coding for the sequences of many proteins, most of which are not being synthesized at any particular moment. The region of DNA on the chromosome that codes for the sequence of a single polypeptide is called a *gene*.[6] In order to *express* a gene (the process whereby the information in a gene is used to synthesize new protein), a copy of the gene is first made as a molecule of RNA (ribonucleic acid).

RNA is a molecule that closely resembles DNA. It differs, however in that it contains a different sugar (ribose instead of deoxyribose) and the base thymine (T) of DNA is replaced in RNA by the structurally similar base, uracil (U). Making an RNA copy of DNA is called *transcription*. The transcribed RNA copy contains sequences of A, U, C, and G that carry the same information as the sequence of A, T, C, and G in the DNA. That RNA molecule, called *messenger RNA*, then moves to a location in the cell where proteins are synthesized.

The code whereby a sequence of nucleotides along an RNA molecule is translated into a sequence of amino acids in a protein (i.e., the "genetic code") is based on serially reading groups of three adjacent nucleotides. Each combination of three adjacent nucleotides, called a *codon*, specifies a particular amino acid. For example, the codon U-G-G in a messenger RNA molecule specifies that there will be a tryptophan molecule in the corresponding location in the corresponding polypeptide. The four bases A, G, C and U can be combined as triplets in 64 different ways, but there are only 20 amino acids to be coded. Thus, most amino acids are coded for by more than one codon. For example, both U-A-U and U-A-C code for tyrosine, and there are six different codons that code for leucine. There are also three codons that do not code for any amino acid (namely, U-A-A, U-G-A, and U-A-G). Like periods at the end of a sentence, these sequences signal the end of the polypeptide chain, and they are therefore called *stop codons*.

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[1] Basic background information about molecular biology and genetic engineering, can be found in Alberts, Bray, Lewis, Raff, Roberts & Watson, *The Molecular Biology of the Cell*, 1-253, 385-481 (1983) [hereinafter *The Cell*]; Watson, Hopkins, Roberts, Steitz & Weiner, *The Molecular Biology of the Gene*, Vol. 1 (4th ed., 1987) 3-502 [hereinafter *The Gene*]. These standard textbooks were used to supplement the information in the glossary supplied by appellants. The description here is necessarily simplified and omits important facts and concepts that are not necessary for the analysis of this case.

[2] There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

[3] Proteins are often loosely called *peptides*, but technically proteins are only the larger peptides with chains of at least 50 amino acids, and more typically hundreds of amino acids. Some proteins consist of several polypeptide chains bound together covalently or noncovalently. The term "peptide" is broader than "protein" and also includes small chains of amino acids linked by peptide bonds, some as small as two amino acids. Certain small peptides have commercial or medical significance.

[4] Polypeptide chains fold up into complex 3-dimensional shapes. It is the shape that actually determines many chemical properties of the protein. However, the configuration of a protein molecule is determined by its amino acid sequence. *The Cell* at 111-12; *The Gene* at 50-54.

[5] The sugar in DNA is deoxyribose, while the sugar in RNA, *infra*, is ribose. The sugar and phosphate groups are linked covalently to those of adjacent nucleotides to form the backbone of the long unbranched DNA molecule. The bases project from the chain, and serve as the "alphabet" of the genetic code.

DNA molecules actually consist of two chains tightly entwined as a double helix. The chains are not identical but instead are complementary: each A on one chain is paired with a T on the other chain, and each C has a corresponding G. The chains are held together by noncovalent bonds between these complementary bases. This double helical structure plays an essential role in the replication of DNA and the transmission of genetic information. *See generally The Cell* at 98-106; *The Gene* at 65-79. However, the information of only one strand is used for directing protein synthesis, and it is not necessary to discuss the implication of the double-stranded structure of DNA here. RNA molecules, *infra*, are single stranded.

[6] Chromosomes also contain regions of DNA that are not part of genes, i.e., do not code for the sequence of amino acids in proteins. These include sections of DNA adjacent to genes that are involved in the control of transcription, *infra*, and regions of unknown function.

The cellular machinery involved in synthesizing proteins is quite complicated, and centers around large structures called *ribosomes* that bind to the messenger RNA. The ribosomes and associated molecules "read" the information in the messenger RNA molecule, literally shifting along the strand of RNA three nucleotides at a time, adding the amino acid specified by that codon to a growing polypeptide chain that is also attached to the ribosome. When a stop codon is reached, the polypeptide chain is complete and detaches from the ribosome.

The conversion of the information from a sequence of codons in an RNA molecule into the sequence of amino acids in a newly synthesized polypeptide is called *translation*. A messenger RNA molecule is typically reused to make many copies of the same protein. Synthesis of a protein is usually terminated by destroying the messenger RNA. (The information for making more of that protein remains stored in DNA in the chromosomes.)

The translation of messenger RNA begins at a specific sequence of nucleotides that bind the RNA to the ribosome and specify which is the first codon that is to be translated. Translation then proceeds by reading nucleotides, three at a time, until a stop codon is reached. If some error were to occur that shifts the frame in which the nucleotides are read by one or two nucleotides, all of the codons after this shift would be misread. For example, the sequence of codons [. . .*C-U-C-A-G-C-G-U-U-A-C-C-A*. . .] codes for the chain of amino acids [. . .leucine-serine-valine-threonine-. . .]. If the reading of these groups of three nucleotides is displaced by one nucleotide, such as [. . .*C-U-C-A-G-C-G-U-U-A-C-C-A*. . .], the resulting peptide chain would consist of [. . .serine-alanine-leucine-proline. . .]. This would be an entirely different peptide, and most probably an undesirable and useless one. Synthesis of a particular protein requires that the correct register or *reading frame* be maintained as the codons in the RNA are translated.

The function of messenger RNA is to carry genetic information (transcribed from DNA) to the protein synthetic machinery of a cell where its information is translated into the amino acid sequence of a protein. However, some kinds of RNA have other roles. For example, ribosomes contain several large strands of RNA that serve a structural function (*ribosomal RNA*). Chromosomes contain regions of DNA that code for the nucleotide sequences of structural RNAs and these sequences are transcribed to manufacture those RNAs. The DNA sequences coding for structural RNAs are still called genes even though the nucleotide sequence of the structural RNA is never translated into protein.

Man, other animals, plants, protozoa, and yeast are *eucaryotic* (or eukaryotic) organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus. Bacteria (*procaryotic* or prokaryotic organisms) have a different organization. Their DNA, usually a circular loop, is not contained in any specialized compartment. Despite the incredible differences between them, all organisms, whether eucaryote or procaryote, whether man or mouse or lowly bacterium, use the same molecular rules to make proteins under the control of genes. In all organisms, codons in DNA are transcribed into codons in RNA which is translated on ribosomes into polypeptides according to the same genetic code. Thus, if a gene from a man is transferred into a bacterium, the bacterium can manufacture the human protein. Since most commercially valuable proteins come from man or other eucaryotes while bacteria are essentially little biochemical factories that can be grown in huge quantities, one strategy for manufacturing a desired protein (for example, insulin) is to transfer the gene coding for the protein from the eucaryotic cell where the gene normally occurs into a bacterium.

Bacteria containing genes from a foreign source (*heterologous* genes) integrated into their own genetic makeup are said to be *transformed*. When transformed bacteria grow and divide, the inserted heterologous genes, like all the other genes that are normally present in the bacterium (*indigenous* genes), are replicated and passed on to succeeding generations. One can produce large quantities of transformed bacteria that contain transplanted heterologous genes. The process of making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into procaryotic cells and then growing those cells is called *cloning* the gene. After growing sufficient quantities of the transformed bacteria, the biotechnologist must induce the transformed bacteria to *express* the cloned gene and make useful quantities of the protein. This is the purpose of the claimed invention.

In order to make a selected protein by expressing its cloned gene in bacteria, several technical hurdles must be overcome. First the gene coding for the specific protein must be isolated for cloning. This is a formidable task, but recombinant DNA technology has armed the genetic engineer with a variety of

techniques to accomplish it.[7] Next the isolated gene must be introduced into the host bacterium. This can be done by incorporating the gene into a cloning vector. A *cloning vector* is a piece of DNA that can be introduced into bacteria and will then replicate itself as the bacterial cells grow and divide. Bacteriophage (viruses that infect bacteria) can be used as cloning vectors, but plasmids were the type used by appellants. A *plasmid* is a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates like a chromosome. It is like a tiny auxilliary chromosome containing only a few genes. Because of their small size, plasmids are convenient for the molecular biologist to isolate and work with. Recombinant DNA technology can be used to modify plasmids by splicing in cloned eucaryotic genes and other useful segments of DNA containing control sequences. Short pieces of DNA can even be designed to have desired nucleotide sequences, synthesized chemically, and spliced into the plasmid. One use of such chemically synthesized linkers is to insure that the inserted gene has the same reading frame as the rest of the plasmid; this is a teaching of the Bahl reference cited against appellants. A plasmid constructed by the molecular geneticist can be inserted into bacteria, where it replicates as the bacteria grow.

Even after a cloned heterologous gene has been successfully inserted into bacteria using a plasmid as a cloning vector, and replicates as the bacteria grow, there is no guarantee that the gene will be expressed, i.e., transcribed and translated into protein. A bacterium such as *E. coli* (the species of bacterium used by appellants) has genes for several thousand proteins. At any given moment many of those genes are not expressed at all. The genetic engineer needs a method to "turn on" the cloned gene and force it to be expressed. This is the problem appellants worked to solve.

II. *Prior art*

Appellants sought to control the expression of cloned heterologous genes inserted into bacteria. They reported the results of their early efforts in a publication, the three authors of which included two of the three coinventor-appellants (the Polisky reference[8]), that is undisputed prior art against them. Their strategy was to link the foreign gene to a highly regulated indigenous gene. Turning on expression of the indigenous gene by normal control mechanisms of the host would cause expression of the linked heterologous gene.

As a controllable indigenous gene, the researchers chose a gene in the bacterium *E. coli* that makes beta-galactosidase. *Beta-galactosidase* is an enzyme needed to digest the sugar, lactose (milk sugar). When *E. coli* grows in a medium that contains no lactose, it does not make beta-galactosidase. If lactose is added to the medium, the gene coding for beta galactosidase is expressed. The bacterial cell makes beta-galactosidase and is then able to use lactose as a food source. When lactose is no longer available, the cell again stops expressing the gene for beta galactosidase.

The molecular mechanisms through which the presence of lactose turns on expression of the beta-galactosidase gene has been studied in detail, and is one of the best understood examples of how gene expression is regulated on the molecular level. The beta-galactosidase gene is controlled by segments of DNA adjacent to the gene. These *regulatory DNA sequences* (the general term used in Claim 1) include the *operator* and *promoter* sequences (specified in Claim 2).[9] The researchers constructed a plasmid containing the beta-galactosidase gene with its operator and promoter. This gene (with its regulatory sequences) was removed from the chromosome of *E. coli* where it is normally found and was transplanted to a plasmid that could be conveniently manipulated.

Restriction endonucleases are useful tools in genetic engineering. These enzymes cut strands of DNA, but only at places where a specific sequence of nucleotides is present. For example, one restriction endonuclease, called *EcoRI*, cuts DNA only at sites where

[7] See *The Cell* at 185–194; *The Gene* at 208–10.

[8] Polisky, Bishop & Gelfand, *A plasmid cloning vehicle allowing regulated expression of eukaryotic DNA in bacteria*, 73 Proc. Nat'l Acad. Sci. USA 3900 (1976).

[9] The *promoter* is a sequence of nucleotides where the enzyme that synthesizes RNA, *RNA polymerase*, attaches to the DNA to start the transcription of the beta-galactosidase gene. The *operator* is an overlapping DNA sequence that binds a small protein present in the cell, the lactose repressor protein. The lactose repressor protein binds to the operator and physically blocks the RNA polymerase from properly attaching to the promoter so that transcription cannot proceed. Lactose molecules interact with the lactose repressor protein and cause it to change its shape; after this change in shape it moves out of the way and no longer prevents the RNA polymerase from binding to the promoter. Messenger RNA coding for beta-galactosidase can then be transcribed. *See generally The Cell* at 438–39; *The Gene* at 474–80.

he nucleotide sequence is [. . .-G-A-A-T-T-C-. . .]. With restriction enzymes the genetic engineer can cut a strand of DNA at very specific sites into just a few pieces. With the help of "repair" enzymes, other pieces of DNA can be spliced onto the cut ends. The investigators found that the plasmid which they had constructed contained only two sequences that were cut by EcoRI. They were able to eliminate one of these sites that was unwanted. They were then left with a plasmid containing the beta-galactosidase gene with its regulatory sequences, and a single EcoRI site that was within the beta-galactosidase gene and close to its stop codon. They named this plasmid that they had constructed pBGP120.

The next step was to cut the plasmid open at its EcoRI site and insert a heterologous gene from another organism. The particular heterologous gene they chose to splice in was a segment of DNA from a frog that coded for ribosomal RNA. The frog gene was chosen as a test gene for reasons of convenience and availability. The new plasmid created by inserting the frog gene was similar to pBGP120, but its beta-galactosidase gene was incomplete. Some codons including the stop codon were missing from its end, which instead continued on with the sequence of the frog ribosomal RNA gene. The investigators named this new plasmid pBGP123. They inserted this plasmid back into *E. coli* and grew sufficient quantities for study. They then fed the *E. coli* with lactose. As they had intended, the lactose turned on transcription of the beta-galactosidase gene in the plasmid. RNA polymerase moved along the plasmid producing a strange new kind of RNA: Each long strand of RNA first contained codons for the messenger RNA for beta-galactosidase and then continued without interruption with the codons for the frog ribosomal RNA. Thus, there was *readthrough* transcription in which the RNA polymerase first transcribed the indigenous (beta-galactosidase) gene and then "read through," i.e., continued into and through the adjacent heterologous (frog ribosomal RNA) gene. Although the RNA produced was a hybrid, it nevertheless contained a nucleotide sequence dictated by DNA from a frog. The researchers had achieved the first controlled transcription of an animal gene inside a bacterium.

The researchers had used a gene coding for a ribosomal RNA as their heterologous test gene. Ribosomal RNA is not normally translated into protein. Nevertheless, they were obviously interested in using their approach to make heterologous proteins in bacteria. They therefore examined the beta-galactosidase made by their transformed bacteria. Patrick O'Farrell, who was not a coauthor of the Polisky paper but was to become a coinventor in the patent application, joined as a collaborator. They found that beta-galactosidase from the transformed bacteria had a higher molecular weight than was normal. They concluded that the bacteria must have used their strange new hybrid RNA like any other messenger RNA and translated it into protein. When the machinery of protein synthesis reached the premature end of the sequence coding for beta-galactosidase it continued right on, three nucleotides at a time, adding whatever amino acid was coded for by those nucleotides, until a triplet was reached with the sequence of a stop codon. The resulting polypeptide chains had more amino acids than normal beta-galactosidase, and thus a higher molecular weight. The researchers published their preliminary results in the Polisky article. They wrote:

> [I]f the normal translational stop signals for [beta]-galactosidase are missing in pBGP120, in-phase translational readthrough into adjacent inserted sequences might occur, resulting in a significant increase in the size of the [beta]-galactosidase polypeptide subunit. In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of *Xenopus* [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Polisky at 3904.

Since ribosomal RNA is never translated in normal cells, the polypeptide chain produced by translating that chain was not a naturally occurring, identified protein. The authors of the Polisky paper explicitly pointed out that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a "fused protein" consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain:

> It would be interesting to examine the expression of a normally translated eukaryotic sequence in pBGP120. If an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide. In the absence of an independent ribosome binding site, the eukaryotic sequence would be translated to yield a peptide covalently linked to [beta]-galactosidase. The extent of readthrough translation under *lac* control will depend on the number of translatable codons between the EcoRI site and the first in-phase nonsense [i.e., stop] codon in the inserted sequence.

Id.

III. *The Claimed Invention*

Referring back to Claims 1 through 3, it can be seen that virtually everything in the claims was present in the prior art Polisky article. The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. Ribosomal RNA gene is not normally translated into protein, so expression of the heterologous gene was studied mainly in terms of transcription into RNA. Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

Appellants reduced their invention to practice some time in 1976 and reported their results in a paper that was published in 1978.[10] During 1977 they communicated their results to another group of researchers who used the readthrough translation approach to achieve the first synthesis of a human protein in bacteria.[11] Appellants filed an application to patent their invention on August 9, 1978, of which the application on appeal is a division.

IV. *The Obviousness Rejection*

The application was rejected under 35 USC 103. The position of the examiner and the Board is, simply, that so much of the appellant's method was revealed in the Polisky reference that making a protein by substituting its gene for the ribosomal RNA gene in Polisky (as suggested by Polisky) would have been obvious to one of ordinary skill in the art at the time that the invention was made.

The claims specify that the heterologous gene should be inserted into the plasmid in the same orientation and with the same reading frame as the preceding portion of the indigenous gene. In view of this limitation, the §103 rejection was based either on Polisky alone (supplemented by the fact that the importance of orientation and reading frame was well known in the prior art) or in combination with the Bahl reference which describes a general method for inserting a piece of chemically synthesized DNA into a plasmid. Bahl teaches that this technique could be used to shift the sequence of DNA inserted into a plasmid into the proper reading frame.

Appellants argue that at the time the Polisky article was published, there was significant unpredictability in the field of molecular biology so that the Polisky article would not have rendered the claimed method obvious to one of ordinary skill in the art. Even though there was speculation in the article that genes coding for proteins could be substituted for the ribosomal RNA gene and would be expressed as readthrough translation into the protein, this had never been done. Appellants say that it was not yet certain whether a heterologous protein could actually be produced in bacteria, and if it could, whether additional mechanisms or methods would be required. They contend

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[10] O'Farrell, Polisk & Gelfand, *Regulated expression by readthrough translation from a plasmid-encoded beta-galactosidase*, 134 J. Bacteriol. 645 (1978). The heterologous genes expressed in these studies were not predetermined, but were instead unidentified genes of unknown origin. The authors speculated that they were probably genes from *E. coli* that were contaminants in the source of beta-galactosidase genes. *Id.* at 648

[11] Itakura, Hirose, Crea, Riggs, Heynecker, Bolivar & Boyer, *Expression in Escherichia coli of a chemically synthesized gene for the hormone somatostatin*, 198 Science 1056 (1977). A pioneering accomplishment of the Itakura group is that the gene was not from a human source, but instead was entirely synthesized in the laboratory using chemical methods. It is not clear whether the appellants communicated only the results reported in the Polisky publication or whether they communicated the complete claimed invention.

that without such certainty the predictions in the Polisky paper, which hindsight now shows to have been correct, were merely invitations to those skilled in the art to try to make the claimed invention. They argue that the rejection amounts to the application of a standard of "obvious to try" to the field of molecular biology, a standard which this court and its predecessors have repeatedly rejected as improper grounds for a §103 rejection. *E.g., In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).

Obviousness under §103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 107 S.Ct. 2187 (1987). An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). *See, e.g., Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 958, 1 USPQ2d 1196, 1197 (Fed. Cir. 1986). The scope and content of the prior art and the differences between the prior art and the claimed invention have been examined in sections II and III, *supra*. Appellants say that in 1976 those of ordinary skill in the arts of molecular biology and recombinant DNA technology were research scientists who had "extraordinary skill in relevant arts" and "were among the brightest biologists in the world." Objective evidence of nonobviousness was not argued.

[1] With the statutory factors as expounded by *Graham* in mind and considering all of the evidence, this court must determine the correctness of the board's legal determination that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. We agree with the board that appellants' claimed invention would have been obvious in light of the Polisky reference alone or in combination with Bahl within the meaning of §103. Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

[2] Appellants argue that after the publication of Polisky, successful synthesis of protein was still uncertain. They belittle the predictive value of the observation that expression of the transcribed RNA in Polisky produced beta-galactosidase with a greater than normal molecular weight, arguing that since ribosomal RNA is not normally translated, the polypeptide chains that were added to the end of the beta-galactosidase were "junk" or "nonsense" proteins. This characterization ignores the clear implications of the reported observations. The Polisky study directly proved that a readthrough transcript messenger RNA had been produced. The preliminary observation showed that this messenger RNA was read and used for successful translation. It was well known in the art that ribosomal RNA was made of the same nucleotides as messenger RNA, that any sequence of nucleotides could be read in groups of three as codons, and that reading these codons should specify a polypeptide chain that would elongate until a stop codon was encountered. The preliminary observations thus showed that codons beyond the end of the beta-galactosidase gene were being translated into peptide chains. This would reasonably suggest to one skilled in the art that if the codons inserted beyond the end of the beta-galactosidase gene coded for a "predetermined protein," that protein would be produced. In other words, it would have been obvious and reasonable to conclude from the observation reported in Polisky that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result. The relative shortness of the added chains is also not a source of uncertainty, since one skilled in the art would have known that a random sequence of nucleotides would produce a stop codon before the chain got too long.[12]

Appellants complain that since predetermined proteins had not yet been produced in transformed bacteria, there was uncertainty as to whether this could be done, and that the rejection is thus founded on an impermissible "obvious to try" standard. It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103. However, the meaning of this maxim is sometime lost. Any invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?

[3] The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g., In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USFQ 81, 90-91 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987); *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). Neither of these situations applies here.

[4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co.*, 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); *In re Papesch*, 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). The information in the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success.

Appellants published their pioneering studies of the expression of frog ribosomal RNA genes in bacteria more than a year before they applied for a patent. After providing virtually all of their method to the public without applying for a patent within a year, they foreclosed themselves from obtaining a patent on a method that would have been obvious from their publication to those of ordinary skill in the art, with or without the disclosures of other prior art. The decision of the board is

AFFIRMED.

[12] The patent application indicates that chains as long as 60 amino acids were added, which is hardly a trivial length of polypeptide.

District Court, W.D. Washington

Specialized Electronics Corp. v. Aviation Supplies & Academics Inc.

No. C86-712D

Decided March 23, 1988

PATENTS

1. Patentability/Validity — Obviousness — Secondary considerations (§115.0907)

Patent infringement defendant has failed to sustain its burden of proving, by clear and convincing evidence, that claims for hand-held aircraft navigational computers are invalid for obviousness under 35 USC 103, in view of objective evidence of secondary considerations demonstrating non-obviousness.

2. Infringement — Defenses — Prosecution history estoppel (§120.1105)

Doctrine of prosecution history estoppel applies to arguments narrowing construction of claims even if claims are not amended.

3. Patent construction — Claims — Broad or narrow (§125.1303)

Doctrine of claim differentiation precludes reading into independent claim limitation explicitly set forth in another claim, and such doctrine, although it is useful tool of claim construction, cannot be used to repudiate arguments made to Patent and Trademark Office in order to obtain allowance of asserted claims over prior art.

Particular patents — General and mechanical — Computers

3,979,057, Katz, Aronson, and Turek, self-contained hand-held electronic computer for aircraft navigation problems, claim 27 valid but not infringed.

3,979,058, Katz, Aronson, and Turek, self-contained electronic computer for math-